Advancements in immunotherapy for oropharyngeal cancer: Current landscape and future prospects

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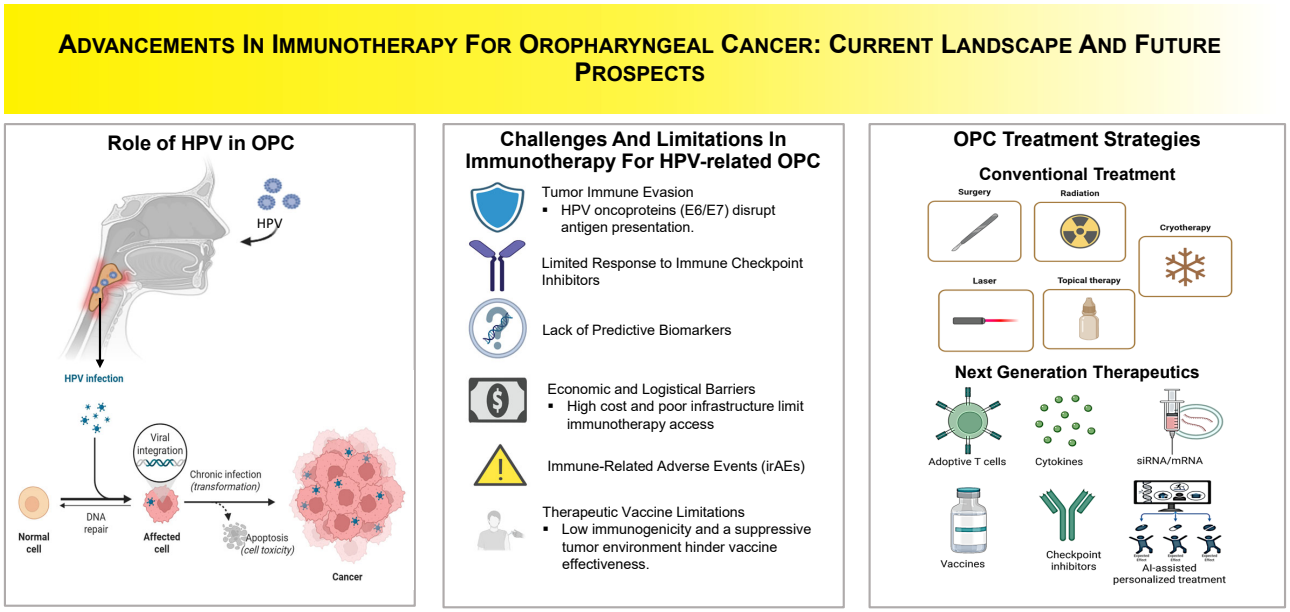
Oropharyngeal cancer (OPC), affecting the tonsils, base of the tongue, and soft palate, has witnessed a notable increase in incidence, particularly among cases linked to human papillomavirus (HPV) infection. This epidemiological shift has led to changes in treatment strategies, with immunotherapy emerging as a promising alternative to conventional modalities such as surgery, radiation, and chemotherapy, which are often associated with significant toxicity. This systematic review aims to evaluate the current landscape of immunotherapeutic interventions in OPC, including immune checkpoint inhibitors, monoclonal antibodies, adoptive T cell therapies, and cancer vaccines. It also explores the influence of HPV status, the development of predictive biomarkers, and the direction of ongoing clinical trials. A comprehensive literature search was conducted using PubMed, Scopus, and Web of Science for studies published between 2010 and 2025. Keywords included "oropharyngeal cancer," "HPV," "immunotherapy," "checkpoint inhibitors," "monoclonal antibodies," "cancer vaccines," and "T cell therapy." Eligible peer-reviewed articles, clinical trials, and reviews focusing on immunotherapy for OPC were included. Data were synthesized based on immunotherapy type, HPV status, clinical outcomes, and biomarker relevance. The review highlights substantial evidence supporting immune checkpoint inhibitors (e.g., anti-PD-1/PD-L1) in improving survival and minimizing adverse effects, particularly in HPV-positive patients. Monoclonal antibodies enhance immune targeting of tumor cells, while cancer vaccines and adoptive T cell therapies show encouraging preliminary outcomes. HPV status and emerging biomarkers are critical in predicting responses and guiding patient-specific therapies. Immunotherapy offers a transformative opportunity in OPC management. Ongoing trials and biomarker research are key to advancing personalized treatment strategies.



Immunotherapy offers promising outcomes for HPV-related OPC but faces hurdles like immune evasion and limited biomarkers. Advancing personalized, combination strategies is key to improving patient care.

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INTRODUCTION

Oropharyngeal cancer (OPC) arises in the oropharynx, which includes the base of the tongue, tonsils, soft palate, and the pharyngeal walls. The majority of OPCs are squamous cell carcinomas (SCCs), originating from the squamous epithelial cells lining these regions[1]. Historically, tobacco and excessive alcohol consumption were the primary risk factors for OPC, with incidence rates higher among older men with prolonged substance use histories[2]. However, in recent decades, the epidemiology of OPC has shifted significantly. Human papillomavirus (HPV), particularly high-risk HPV type 16, has emerged as a leading etiological factor, associated with a distinct subset of OPC cases[1]. This shift has resulted in a changing clinical profile. HPV-positive OPC now predominantly affects younger individuals in their 40s and 50s, many of whom lack significant tobacco or alcohol exposure[3]. Epidemiological data show a 2% annual increase in HPV-related OPC in the United States, with HPV-positive cases currently accounting for 70–80% of all OPC diagnoses in the developed world. According to the American Cancer Society, approximately 54,450 new cases of oral cavity and oropharyngeal cancers were expected in 2023, resulting in 12,230 estimated deaths[4]. The continuing rise of HPV-positive OPC highlights an urgent need for tailored diagnostic and treatment strategies.

Clinically, HPV-positive OPC often presents with persistent sore throat, dysphagia, hoarseness, or palpable neck masses due to lymph node metastasis[5]. Diagnosis is confirmed through clinical examination, biopsy, and advanced imaging such as CT, MRI, and PET scans to evaluate tumor spread[6]. HPV status has become a crucial prognostic and therapeutic determinant. Patients with HPV-positive OPC typically present with earlier-stage disease and respond better to conventional treatments including surgery, radiotherapy, and chemotherapy, resulting in five-year survival rates of 80–90%, compared to 50–60% in HPV-negative cases[7]. This favorable prognosis is attributed to the tumor's immunogenic profile and earlier diagnosis. HPV comprises over 200 related viruses, transmitted primarily through skin-to-skin and oral-genital contact. These viruses are classified as low- or high-risk based on their oncogenic potential[8] (WHO 2024). Low-risk types (e.g., HPV 6 and 11) cause benign lesions such as genital warts, while high-risk types, particularly HPV 16 and 18, are associated with malignant transformation in the cervix, anus, and oropharynx[9]. HPV promotes carcinogenesis through the expression of E6 and E7 oncogenes, which inactivate the tumor suppressor proteins p53 and Rb, respectively, resulting in unregulated cell proliferation and genomic instability[10], shown in Fig. 1.

Persistent infection with high-risk HPV types, particularly in the tonsillar crypts and base of the tongue, facilitates malignant transformation in the oropharynx[11]. HPV-positive OPCs exhibit distinct molecular features, including a lower rate of p53 mutations, high levels of tumor-infiltrating lymphocytes (TILs), and strong expression of HPV-specific neoantigens such as E6 and E7 (ref.[7,12]). These factors contribute to an immune-responsive tumor microenvironment, making HPV-positive OPCs promising targets for immunotherapeutic interventions. The immunogenicity of HPV-positive OPC has led to the development of immune-based therapies such as immune checkpoint inhibitors (ICIs) and therapeutic vaccines targeting HPV oncoproteins. Unlike conventional treatments, immunotherapy leverages the host's immune system to selectively recognize and destroy cancer cells, thereby minimizing collateral damage to healthy tissue[13]. By activating cytotoxic T lymphocytes and enhancing im-

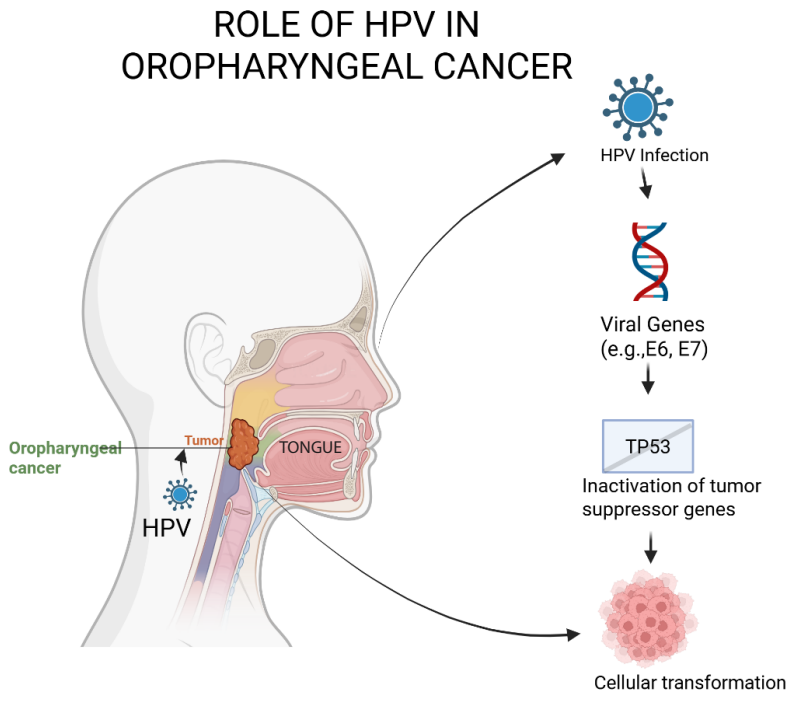

Fig. 1. Role of HPV in oropharyngeal cancer.

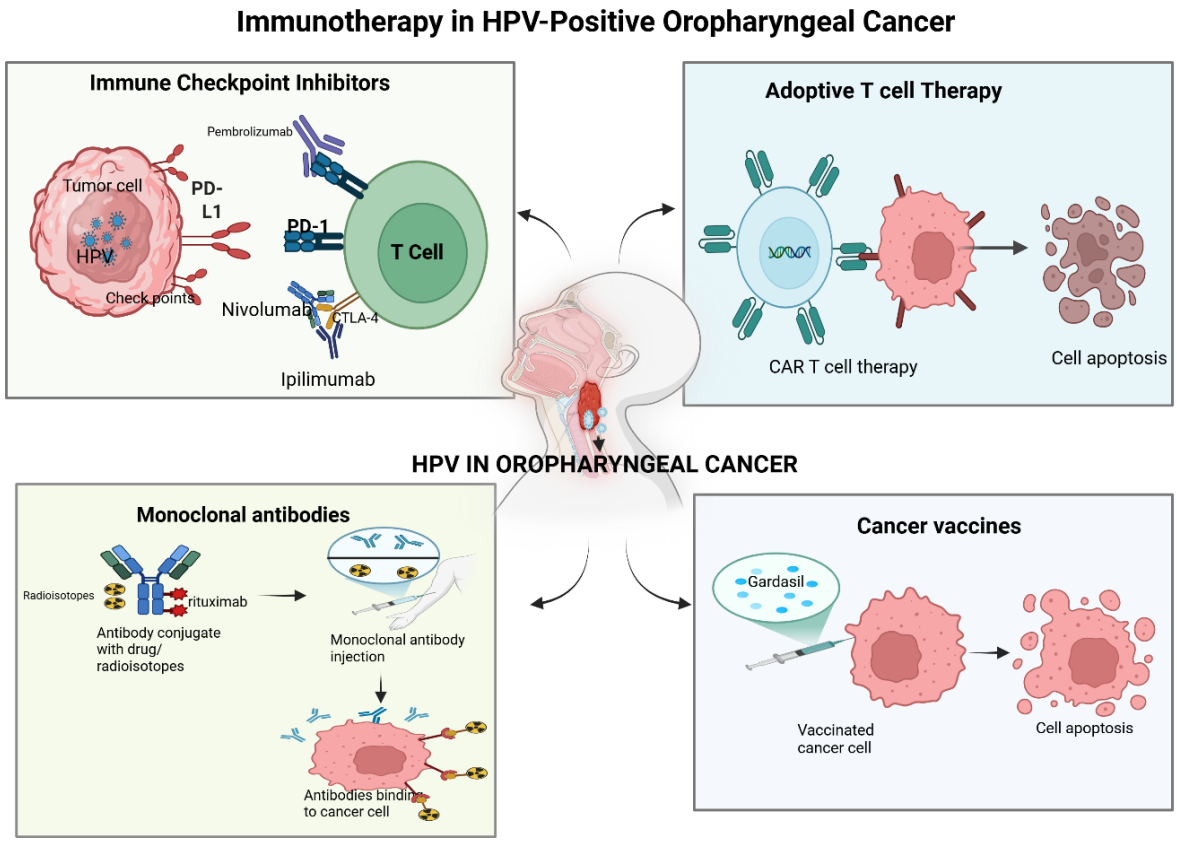

Fig. 2. Immunotherapeutic approaches in HPV positive oropharyngeal cancer.

mune memory, immunotherapies offer durable responses with fewer side effects compared to traditional approaches[14]. Moreover, these therapies hold particular promise for HPV-driven cancers, where the immune system can be primed to target specific viral antigens[15].

In light of the rising incidence of HPV-positive OPC and its unique immunobiological profile, immunotherapy has become a focal point of current research. This review aims to provide an updated overview of advancements in immunotherapeutic strategies for OPC, emphasizing their mechanisms of action, clinical outcomes, and future directions for improving patient care.

IMMUNOTHERAPEUTIC APPROACHES IN OROPHARYNGEAL CANCER

The advent of immunotherapy has revolutionized treatment paradigms for oropharyngeal cancer (OPC), particularly in the HPV-positive subtype, due to its heightened immunogenicity. A range of immunotherapeutic strategies are currently under clinical investigation, showing encouraging outcomes. These include immune checkpoint inhibitors (ICIs), adoptive T cell therapy (ACT), monoclonal antibodies (mAbs), and cancer vaccines[16], illustrated in Fig. 2.

ICIs such as pembrolizumab and nivolumab restore T cell function by blocking inhibitory pathways exploited by tumors, including PD-1 and CTLA-4. CAR-T cell therapy involves engineering a patient's T cells to express chimeric antigen receptors that recognize tumor antigens, proving highly effective in hematologic malignancies. Monoclonal antibodies can directly target tumor-specific antigens or function as antibody-drug conjugates (ADCs), delivering cytotoxic agents to cancer cells. Cancer vaccines and adoptive cell therapies such as tumor-infiltrating lymphocyte (TIL) therapy enhance antigen-specific immune responses, with promising results in HPV-related cancers[17]. This section explores the major immunotherapeutic strategies and their current clinical relevance in OPC.

Immune checkpoint inhibitors: mechanisms and efficacy

Immune checkpoint inhibitors (ICIs) have transformed cancer immunotherapy by targeting key regulatory pathways that tumors exploit to evade immune surveillance. These inhibitors primarily focus on programmed cell death protein 1 (PD-1) and its ligand PD-L1, as well as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), which function as immune checkpoints to maintain self-tolerance and prevent excessive immune activation. Many cancers upregulate PD-L1 or CTLA-4 signalling to suppress T-cell-mediated immune responses, allowing tumor progression. By blocking these inhibitory pathways, ICIs restore T-cell activity, enhancing anti-tumor immunity and leading to prolonged disease control in various malignancies. PD-1 inhibitors such as nivolumab and pembrolizumab, and PD-L1 inhibitors including atezolizumab, durvalumab, and avelumab, have demonstrated significant efficacy in treating non-small cell lung cancer (NSCLC), melanoma, renal cell carcinoma (RCC), head and neck squamous cell carcinoma (HNSCC), and gastric cancer[18]. Similarly, CTLA-4 inhibitors like ipilimumab have shown

remarkable benefits, particularly in melanoma, where combination therapy with PD-1 inhibitors has significantly improved survival outcomes[19].

The effectiveness of ICIs varies depending on tumor immunogenicity, as seen in HPV-positive and HPV-negative OPC. HPV-positive OPC, characterized by high tumor-infiltrating lymphocyte (TIL) density and viral antigen expression, responds favorably to PD-1 inhibitors, as evidenced by clinical trials such as KEYNOTE-012 and CheckMate-141, which reported improved overall survival (OS) and progression-free survival (PFS) in patients with recurrent or metastatic disease[20,21]. In contrast, HPV-negative OPC exhibits lower immunogenicity and greater resistance to ICIs, necessitating combination strategies with chemotherapy or radiotherapy to enhance therapeutic efficacy[22]. The KEYNOTE-048 trial demonstrated that combining pembrolizumab with cytotoxic chemotherapy displaced the EXTREME regimen as the standard of care, with platinum-5-fluorouracil hypothesized to enhance tumor antigen presentation, immunogenic cell death, and CD8+ T-cell infiltration, leading to a robust anti-tumor immune response[16]. The KEYNOTE-048 post hoc analysis showed that first-line pembrolizumab, alone or with chemotherapy, offered sustained survival advantages in recurrent or metastatic head and neck squamous cell carcinoma, especially in patients with higher PD-L1 expression. These therapies also maintained effectiveness when followed by additional treatments[23].

Emerging evidence suggests that chemotherapy can upregulate PD-L1 expression, making PD-1/PD-L1 blockade a rational therapeutic approach. Trials such as DUCRO (NCT03051906) are investigating the combination of durvalumab with cetuximab and radiotherapy in locally advanced HNSCC, while EA 3161 (NCT03811015) evaluates maintenance nivolumab after standard cisplatin chemoradiation in intermediate-risk, HPV-positive OPC (ref.[16]). The Checkmate 651 trial assessed nivolumab plus ipilimumab versus the EXTREME regimen in recurrent/metastatic head and neck squamous cell carcinoma but did not meet its primary overall survival endpoints. While survival improvement was not statistically significant, the immunotherapy combination showed a more favorable safety profile and longer response duration in PD-L1 CPS ≥ 20 patients[24].

Beyond PD-1 and CTLA-4, novel immune checkpoints such as TIGIT, TIM-3, and LAG-3 are gaining interest due to their roles in T-cell exhaustion. These markers are upregulated in HPV-positive HNSCC, likely due to chronic viral infection, and their blockade may provide additional therapeutic benefits[25]. The SKYSCRAPER-09 trial (NCT04665843) is assessing tiragolumab, an anti-TIGIT mAb, in combination with atezolizumab in PD-L1-positive HNSCC, while relatlimab, an anti-LAG-3 mAb, is being studied alongside nivolumab in NCT04326257. TIM-3 inhibition is also under active investigation, with TSR-022 (NCT02817633) and MBG453 (NCT02608268) showing promise in early-phase trials[26]. A study examining TIM-3 expression in 80 HNSCC specimens found that high TIM-3-positive tumor-infiltrating lymphocytes correlated with poor OS, highlighting its potential as a prognostic marker (HR 2.066; 95% CI 2.832–12.230; $P<0.001$) (ref.[27]).

Despite the success of ICIs, challenges such as primary and acquired resistance, immune-related adverse events (irAEs), and the need for predictive biomarkers remain significant hurdles. Ongoing research aims to optimize treatment strategies through biomarker-driven approaches, combination therapies, and personalized medicine to maximize the clinical benefits of ICIs and overcome resistance mechanisms[13]. As immunotherapy continues to evolve, integrating ICIs with other therapeutic modalities holds great promise in improving cancer treatment outcomes. A summary of key immune checkpoint inhibitors, their targets, approved indications, and relevant clinical trials is provided in Table 1.

Adoptive T cell therapy and its applications

Adoptive T cell therapy (ACT) is a potent form of immunotherapy that enhances the body's anti-tumor response by isolating, expanding, and reinfusing autologous or genetically modified T cells[28]. Among ACT strategies, tumor-infiltrating lymphocyte (TIL) therapy is notable for utilizing T cells that naturally target tumor antigens, especially effective in tumors with high mutational burdens, such as melanoma[29]. TIL therapy is now being evaluated for other solid tumors, including cervical cancer, NSCLC, and HNSCC. Preconditioning regimens using lymphodepleting chemotherapy enhance the effectiveness of TILs

Table 1. Overview of key immune checkpoint inhibitors, their molecular targets, approved indications, and notable clinical trials.

Checkpoint inhibitor	Target	Approved indications	Key clinical trials
Nivolumab	PD-1	NSCLC, Melanoma, RCC, HNSCC	CheckMate-141, CheckMate-651
Pembrolizumab	PD-1	NSCLC, Melanoma, HNSCC, Gastric Cancer	KEYNOTE-012, KEYNOTE-048
Atezolizumab	PD-L1	NSCLC, RCC	SKYSCRAPER-09
Durvalumab	PD-L1	NSCLC, HNSCC	DUCRO, EAGLE
Avelumab	PD-L1	Merkel Cell Carcinoma, RCC	JAVELIN, Recent Phase III Trial
Ipilimumab	CTLA-4	Melanoma	CheckMate-651
Tiragolumab	TIGIT	Under investigation	SKYSCRAPER-09
Relatlimab	LAG-3	Under investigation	NCT04326257
TSR-022	TIM-3	Under investigation	NCT02817633
MBG453	TIM-3	Under investigation	NCT02608268

by reducing immunosuppressive elements in the tumor microenvironment. Combination with ICIs may further prevent T cell exhaustion and prolong therapeutic benefits[30]. In HPV-positive OPC, TILs targeting viral oncoproteins E6 and E7 have shown encouraging outcomes, with some patients achieving objective tumor regression in early-phase trials.

Another transformative ACT approach is chimeric antigen receptor (CAR) T cell therapy, which involves engineering T cells to express synthetic CARs that recognize specific tumor antigens. Unlike TILs, CAR-T cells are not limited by natural antigen recognition, providing enhanced specificity and activity. CAR-T therapy has shown remarkable efficacy in hematologic malignancies such as acute lymphoblastic leukemia (ALL), diffuse large B-cell lymphoma (DLBCL), mantle-cell lymphoma, and chronic lymphocytic leukemia (CLL) (ref.[31]). Despite the success in hematological cancers, translating CAR-T therapy to solid tumors like OPC remains challenging due to factors such as the immunosuppressive tumor microenvironment, antigen heterogeneity, and limited T cell persistence. Current research is focused on improving CAR-T efficacy using dual-targeting CARs, "armored" CARs that secrete immune-stimulatory cytokines, and optimized co-stimulation domains[32].

As ACT continues to evolve, both TIL and CAR-T cell therapies hold significant promise for improving outcomes in patients with OPC, especially in HPV-positive subtypes that present unique tumor antigens[20]. Innovations in ACT also include T cell receptor (TCR)-engineered T cells, which involve introducing a TCR gene specific to tumor-associated antigens into the patient's T cells, allowing them to recognize intracellular antigens presented by Major Histocompatibility Complex (MHC) molecules[33]. Unlike CAR-T cells that primarily target surface antigens, TCR-T cells can access a broader range of targets, including viral oncoproteins such as HPV E6 and E7, which are consistently expressed in HPV-positive OPC (ref.[34]). Clinical trials investigating TCR-T cells targeting HPV16 E6 and E7 have shown early signs of safety and efficacy, further supporting their therapeutic potential. Despite the advancements, ACT faces several limitations in solid tumors like OPC. These include antigen heterogeneity, the immunosuppressive tumor microenvironment, limited T cell trafficking to tumor sites, and immune evasion mechanisms. Furthermore, toxicities such as cytokine release syndrome (CRS) and neurotoxicity, particularly with CAR-T therapy, pose safety concerns and necessitate careful monitoring and the development of safety switches or controllable CAR constructs[35].

To overcome these challenges, combinatorial strategies are under exploration. These include preconditioning regimens, co-administration with checkpoint inhibitors, targeting stromal or immune-suppressive cells, and engineering T cells with enhanced metabolic fitness or resistance to exhaustion. Additionally, allogeneic "off-the-shelf" T cell therapies are emerging as a scalable and potentially more accessible alternative to autologous ACT (ref.[36]). These approaches utilize T cells derived from healthy donors, which are genetically modified to prevent graft-versus-host disease (GVHD) and host immune rejection Technologies such as TALEN or CRISPR-Cas9 are employed to knock out genes like T cell receptor alpha constant (TRAC) and β2-microglobulin, allowing the creation of universal CAR-T cells with minimized immunogenicity[37].

Clinical trials investigating these universal T cells (e.g., UCART19, ALLO-501) have shown promising results in hematologic malignancies, and similar strategies are being explored for solid tumors, including head and neck squamous cell carcinoma (HNSCC) (ref.[38]). For instance,

Table 2. Examples of adoptive T cell therapies in OPC.

ACT Type	Target Antigen / Approach	Cancer Type / Focus	Clinical Trial (Identifier / Sponsor)	Key Findings / Status
TIL Therapy	Naturally occurring tumor-reactive TILs, including HPV-specific T cells	HPV-positive OPC, cervical cancer, NSCLC	NCT01585428 (NIH/NCI)	Demonstrated objective tumor regression in HPV+ solid tumors, including OPC; ongoing investigation
TIL Therapy + ICIs	TILs combined with checkpoint inhibitors (e.g., nivolumab)	Refractory solid tumors including HNSCC	NCT03215810 (MD Anderson)	Investigating whether ICI enhances TIL function and durability; preliminary safety confirmed
CAR-T Cell Therapy	CAR-Ts targeting EGFR, HER2, or B7-H3 in solid tumors	Head and neck cancers (including OPC)	NCT03542799, NCT03618381	Early-phase trials testing safety/feasibility of CAR-Ts in solid tumors; challenges remain in OPC
TCR-Engineered T Cells	TCRs targeting HPV16 E6 and E7 oncoproteins (HLA-A*02:01)	HPV+ cancers: OPC, cervical, anal	NCT02858310 (ImmunoCore)	Promising tumor regression and safety in early-phase trials in HPV16+ OPC and cervical cancer
TCR-T Cells + IL-2 Support	HPV-specific TCR-T cells + IL-2 cytokine support	Advanced HPV+ OPC	NCT02379520 (NCI)	Enhanced persistence and efficacy of TCR-T cells observed; ongoing monitoring for CRS
Allogeneic T Cell Therapy (Off-the-shelf)	Genome-edited universal CAR-T cells (e.g., TALEN or CRISPR-Cas9 based)	Solid tumors including OPC (preclinical/early-phase)	NCT03190278 (Allogene) NCT04696731 (Cellectis)	Early-stage trials exploring feasibility; mostly hematologic to date; expansion to solid tumors anticipated

NCT03190278 and NCT04696731 are early-phase studies assessing the safety and feasibility of genome-edited allogeneic CAR-T cells[39]. Although these trials are currently more advanced in blood cancers, their potential application in HPV-positive OPC is actively being investigated. Overall, adoptive T cell therapies including TILs, CAR-T cells, TCR-engineered T cells, and emerging allogeneic T cell platforms represent a rapidly advancing frontier in immunotherapy for OPC (ref.[40]) (Table 2). These strategies, particularly in HPV-positive tumors, capitalize on the immune system's ability to recognize viral antigens and mediate potent anti-tumor effects. Future developments aimed at enhancing specificity, persistence, safety, and overcoming immunosuppression will be critical to fully realize the therapeutic potential of ACT in head and neck cancers.

Monoclonal antibodies and anti-body drug conjugates

Monoclonal antibodies (mAbs) have emerged as a cornerstone in targeted cancer therapy due to their ability to specifically recognize and bind to tumor-associated antigens, thereby initiating immune-mediated tumor destruction or delivering cytotoxic payloads[41]. In the context of oropharyngeal cancer (OPC), especially HPV-negative subtypes, mAbs offer an effective strategy to target overexpressed receptors such as epidermal growth factor receptor (EGFR) and programmed death-ligand 1 (PD-L1) (ref.[42]).

Cetuximab, a chimeric IgG1 mAb targeting EGFR, is currently approved for the treatment of head and neck squamous cell carcinoma (HNSCC), including OPC. EGFR is overexpressed in over 90% of HNSCCs, and its activation promotes tumor cell proliferation, angiogenesis, and resistance to apoptosis[43]. Cetuximab exerts its therapeutic effects by blocking EGFR signaling and mediating antibody-dependent cellular cytotoxicity (ADCC) through Fcγ receptor engagement on immune effector cells. Clinically, cetuximab is often combined with radiotherapy or chemotherapy and has demonstrated improved overall survival in locoregionally advanced OPC. However, its benefits are limited by acquired resistance, modest response rates, and toxicity profiles, such as severe skin reactions and infusion-related reactions[44]. In recent years, immune checkpoint inhibitors (ICIs) are another class of mAbs that have significantly impacted the treatment of recurrent or metastatic OPC. Antibodies targeting PD-1 (e.g., pembrolizumab, nivolumab) and PD-L1 (e.g., durvalumab) restore T cell activity by blocking inhibitory signals within the tumor microenvironment[45]. Clinical trials such as KEYNOTE-048 have shown that pembrolizumab, alone or in combination with chemotherapy, improves survival in patients with PD-L1-positive HNSCC, including OPC (ref.[46]). These results highlight the utility of PD-1/PD-L1 blockade in reversing T cell exhaustion and promoting anti-tumor immunity, especially in tumors with an inflamed immune phenotype.

Antibody-drug conjugates (ADCs) represent a novel and promising extension of mAb therapy by linking monoclonal antibodies to potent cytotoxic agents via chemical linkers. ADCs enable targeted delivery of chemotherapy directly to tumor cells, minimizing systemic toxicity[47]. One example under investigation in HNSCC is tisotumab vedotin, an ADC targeting tissue factor (TF), which is overexpressed in several epithelial malignancies[48]. While not yet approved for OPC, early-phase trials have demonstrated encouraging activity in solid tumors, warranting further investigation in head and neck cancers. Despite the success of mAb-based therapies, several barriers remain, including tumor antigen heterogeneity, immunosuppressive microenvironment, and development of neutralizing antibodies. Additionally, the lack of predictive biomarkers for therapeutic response complicates patient selection and treatment optimization[49]. Ongoing efforts focus on combining mAbs or ADCs with other modalities such as immune checkpoint inhibitors, radiation, or targeted small molecule inhibitors to enhance efficacy and overcome resistance. Table 3 summarizes examples of monoclonal antibodies and ADCs currently approved or under investigation for OPC and HNSCC treatment[50].

Cancer vaccines

Cancer vaccines represent a promising immunotherapeutic approach designed to elicit or amplify a patient's immune response specifically against tumor-associated antigens (TAAs) or tumor-specific antigens (TSAs) (ref.[51]). In the context of oropharyngeal cancer (OPC), particularly HPV-positive subtypes, therapeutic vaccines offer a unique opportunity to harness the immune system against viral oncoproteins such as E6 and E7 of human papillomavirus type 16 (HPV-16) (ref.[52]). These oncoproteins are consistently expressed in HPV-driven tumors and are essential for malignant transformation, making them ideal targets for immune intervention. Several types of cancer vaccines are under investigation for OPC, including peptide-based vaccines, DNA vaccines, RNA vaccines, and dendritic cell (DC)-based vaccines (Table 4) (ref.[53]). Peptide vaccines consisting of synthetic short epitopes derived from HPV-16 E6 and E7 have been shown to induce antigen-specific CD8 cytotoxic T lymphocyte (CTL) responses. One such vaccine, ISA101, has been evaluated

Table 3. Examples of monoclonal antibodies and antibody-drug conjugates used or investigated in OPC and HNSCC.

Agent	Target	Type	Clinical Indication	Mechanism of Action	Ref.
Cetuximab/ Imgatuzumab	EGFR	Monoclonal antibody	Approved for OPC and HNSCC	EGFR inhibition, ADCC	50
Tisotumab vedotin	Tissue Factor (TF)	Antibody-drug conjugate	Investigational in solid tumors including HNSCC	Delivers MMAE payload to TF-expressing cells, induces apoptosis	48

Table 4. Summary of cancer vaccines under investigation for oropharyngeal cancer (OPC).

Vaccine type	Target antigen	Mechanism of action	Clinical applications	Ref.
Peptide-based vaccines	HPV16 E6 and E7 (e.g., ISA101)	Induces antigen-specific CD8 T cell responses	Enhances T cell infiltration; improved outcomes when combined with nivolumab	58
DNA vaccines	HPV16/18 E6/E7 (e.g., MEDI0457)	Stimulates cellular and humoral responses via electroporation delivery	Demonstrated safety and immunogenicity in early-phase OPC trials	59
RNA vaccines	HPV E6/E7	Activates dendritic cells and primes CD8 T cells using LNP delivery	Under investigation; benefits from rapid design, scalability, and low integration risk	Ongoing studies; post-COVID platforms
Dendritic cell vaccines	HPV antigens (E6/E7), tumor lysates	Enhances antigen presentation and activates adaptive immune responses	Personalized immunotherapy; promising but labor-intensive and costly	60

in combination with immune checkpoint blockade (e.g., nivolumab) in HPV-positive cancers, demonstrating enhanced T cell infiltration and clinical responses[54].

DNA vaccines, such as MEDI0457, encode HPV-16/18 E6/E7 fusion proteins and are delivered via electroporation to enhance uptake and expression. In early-phase clinical trials, MEDI0457 has shown favorable safety profiles and immunogenicity in HPV-associated HNSCC, with durable immune responses observed in vaccinated patients[55]. DNA vaccines are attractive due to their stability, ease of manufacturing, and ability to induce both humoral and cellular immune responses. RNA-based vaccines, especially those utilizing lipid nanoparticle (LNP) formulations, have gained momentum following the success of mRNA vaccines against COVID-19. mRNA vaccines targeting E6/E7 of HPV are currently being investigated for their ability to activate dendritic cells and prime CD8 T cells in situ[56]. These platforms offer rapid design, scalable production, and transient expression, which reduce the risk of genomic integration. Dendritic cell vaccines involve the *ex vivo* loading of patient-derived DCs with HPV antigens, followed by reinfusion into the patient[57]. This strategy has demonstrated promising immunological and clinical activity in small-scale studies, although the approach is labor-intensive and costly. Advances in DC maturation protocols and antigen loading techniques continue to improve their immunogenicity and clinical applicability.

While therapeutic vaccines for HPV-positive OPC show considerable promise, challenges remain. These include limited immunogenicity in some patients, immune evasion by tumors, and immune suppression within the tumor microenvironment. Additionally, for HPV-negative OPC, the lack of defined tumor-specific antigens makes vaccine development more complex and less targeted. Combination approaches such as vaccines with immune checkpoint inhibitors or conventional treatments like radiotherapy are currently being explored to enhance vaccine efficacy and promote long-term immune memory. In summary, cancer vaccines offer a safe and tumor-specific strategy to induce robust anti-tumor immunity in OPC, particularly in HPV-positive cases. Ongoing clinical trials and advancements in vaccine platforms are expected to play a critical role in establishing their utility in future OPC treatment paradigms.

HPV AND ITS IMPACT ON IMMUNOTHERAPY RESPONSE

Human papillomavirus (HPV)-associated oropharyngeal cancer (OPC) exhibits distinct biological and immunological characteristics that affect its responsiveness to immunotherapy. This section discusses the role of HPV in OPC biology, its influence on immunotherapy efficacy, and the clinical outcomes associated with HPV-related OPC.

Role of HPV in oropharyngeal cancer biology

The etiological role of HPV in oropharyngeal squamous cell carcinoma (OPSCC) was initially supported by studies utilizing molecular techniques such as PCR and in situ hybridization in the late 1990s and early 2000s. Presently, HPV testing is recommended for all oropharyngeal tumors by the National Comprehensive Cancer Network (NCCN), and HPV status is used as a stratification factor in clinical trials by institutions like the US National Cancer Institute (NCI) and Cancer Therapy Evaluation Program (CTEP) (ref.[61]). As mentioned, HPV-driven OPC is primarily associated with high-risk genotypes, especially HPV-16, which integrates into the host genome and expresses oncogenic proteins E6 and E7. Compared to HPV-negative OPCs, HPV-positive tumors display lower mutational burdens but higher immunogenicity due to viral antigens. They also exhibit elevated expression of immune checkpoint molecules like PD-L1, promoting immune evasion. Importantly, HPV-positive OPCs demonstrate increased infiltration of tumor-infiltrating lymphocytes (TILs), particularly CD8+ cytotoxic T cells, contributing to an inflamed tumor microenvironment an ideal target for immunotherapeutic strategies such as PD-1/PD-L1 inhibitors[62].

Epidemiological studies reveal a rising trend in HPV-related oropharyngeal cancers, notably in the tonsillar and base of tongue regions. In the US, the incidence among individuals aged 20–44 years increased by 3.9% in men

and 2.1% in women between 1973 and 2004. Similar increases were observed in Sweden, where tonsillar cancer incidence tripled between 1970 and 2001. From 1988 to 2004, HPV-positive OPC incidence surged by 225% (ref.[63]). HPV shows a preference for the oropharynx, possibly due to the presence of transitional mucosa, particularly in the tonsillar crypts, which resemble cervical mucosa. The persistence of HPV-16 in this epithelium is likely supported by these histological features. Genomic studies indicate that HPV-positive OPSCCs with transcriptionally active viral DNA exhibit occasional chromosomal loss and allelic imbalance, contrasting with the large-scale deletions found in HPV-negative tumors[64].

Clinically, HPV-positive OPCs usually present with early T stages (T1–T2) but more advanced nodal involvement, often with cystic and multi-level nodes. Histologically, these tumors are often poorly differentiated, non-keratinizing, or basaloid. Distant metastases are less common and follow distinct patterns compared to HPV-negative tumors. The prognosis of HPV-positive OPC is generally favorable, with a 28% lower risk of death and a 49% lower risk of recurrence[65]. The rarity of secondary primary tumors (SPTs), lower genetic alteration rates, and higher radiosensitivity possibly due to intact apoptotic pathways contribute to better survival outcomes. An intact immune response to viral antigens may further enhance therapeutic efficacy. Additionally, favorable outcomes are associated with factors like younger age, better performance status, low EGFR expression, and high p16 expression. In contrast, HPV-negative patients often have worse prognoses and require more intensive treatment[66-67]. Given these findings, HPV status plays a crucial role in clinical decision-making, particularly in selecting patients for less aggressive, non-surgical treatment approaches.

How HPV-positive OPC affects immunotherapy efficacy

The unique immunological landscape of HPV-positive oropharyngeal cancer (OPC) significantly influences its responsiveness to immunotherapy, particularly immune checkpoint inhibitors (ICIs). The presence of viral oncoproteins, such as E6 and E7, leads to the formation of viral neoantigens that are recognized by the host immune system, thereby enhancing immune surveillance. These neoantigens elicit strong adaptive immune responses, particularly the activation of cytotoxic CD8+ T cells and the promotion of Th1-skewed immunity[68]. This antigenic landscape is largely absent in HPV-negative OPC, where carcinogenesis is driven more by mutagens such as tobacco and alcohol, resulting in more heterogeneous tumor antigens and a suppressed immune microenvironment[69].

HPV-positive tumors have higher cytolytic activity scores and increased expression of genes related to T-cell exhaustion (e.g., PD-1, TIM-3, and LAG-3), indicating that while T cells are active, they are also chronically stimulated and can benefit from immune rejuvenation through checkpoint blockade[16]. Comparatively, HPV-negative HNSCCs often exhibit an immunosuppressive phenotype, with fewer TILs, higher numbers of M2-polarized macrophages, and greater expression of TGF-β and VEGF, which hinder effective immune responses[69]. This contrast in TIME between HPV-positive and HPV-negative tumors likely contributes to the differential responses seen with ICIs.

These immunological insights are supported by pivotal clinical trials. The Checkmate 141 trial evaluated nivolumab in recurrent/metastatic HNSCC and reported a significant improvement in overall survival (OS) in the treatment arm compared to standard therapy (7.5 vs. 5.1 months; HR=0.70; *P*=0.01). Notably, the HPV-positive subgroup showed a median OS of 9.1 months vs. 4.4 months in the control, suggesting a better response to PD-1 inhibition in this population[70]. Similarly, the KEYNOTE-048 trial examined pembrolizumab, alone or in combination with chemotherapy, versus standard EXTREME regimen in first-line treatment for recurrent/metastatic HNSCC. Among HPV-positive patients, pembrolizumab monotherapy resulted in a median OS of 14.9 months, compared to 10.8 months with the EXTREME regimen. The combination arm (pembrolizumab + chemotherapy) further increased OS to 17.6 months[46]. These data underscore the relevance of HPV status as a predictive biomarker in immunotherapy planning.

Furthermore, an analysis by Cillo et al.[71] using The Cancer Genome Atlas (TCGA) data showed that HPV-positive HNSCCs had higher T-cell receptor (TCR) clonality and diversity, both of which are associated with more robust and sustained anti-tumor immune responses again reinforcing the biological rationale for their better immunotherapy outcomes. However, it is important to note that not all HPV-positive tumors respond equally. Some studies suggest that tumor mutational burden (TMB) and the expression of other immune checkpoints (e.g., TIGIT, CTLA-4) may further stratify response and merit inclusion in predictive models for immunotherapy[72,73]. The enhanced immunogenicity of HPV-positive OPC characterized by viral neoantigens, a robust immune infiltrate, and high checkpoint molecule expression makes it particularly amenable to immune checkpoint blockade[74]. These findings support ongoing efforts to integrate biomarker-driven immunotherapy into the treatment algorithm for HPV-associated OPC, aiming to maximize clinical benefit while reducing treatment-related toxicity.

Clinical outcomes based on HPV-related OPC

Human papillomavirus related oropharyngeal carcinoma is typically associated with favorable clinical outcomes compared to HPV-negative OPC. This improved prognosis is largely attributed to the distinct tumor biology of HPV-positive tumors and their enhanced response to chemoradiotherapy[75]. However, emerging evidence suggests that not all HPV-related OPCs behave uniformly, particularly when comparing tumors driven by HPV16 to those caused by other high-risk HPV genotypes. Studies have consistently shown that HPV16-positive OPC patients demonstrate significantly higher overall survival (OS) rates compared to those with non-HPV16 subtypes. A meta-analysis conducted by Shenker et al.[76] supports this, revealing that five-year survival is notably higher in HPV16-positive patients, whereas non-HPV16 subtypes exhibit more variable and often poorer outcomes. Similarly,

studies reported that patients with non-HPV16 OPC have reduced OS and a trend toward lower recurrence-free survival, although the latter did not reach statistical significance[62]. These findings suggest that non-HPV16 subtypes may not respond as favorably to standard treatment protocols and may require tailored therapeutic strategies.

In clinical practice, p16 immunohistochemistry (IHC) is widely used as a surrogate marker for HPV-related OPC due to its accessibility and cost-effectiveness. Nonetheless, this approach has limitations, including the potential for both false positives and false negatives[77]. While p16 positivity is strongly correlated with HPV16-related OPC, its predictive value diminishes for non-HPV16 subtypes, which often exhibit lower or inconsistent p16 expression. This variation can result in misclassification of HPV status, ultimately affecting prognostic accuracy and therapeutic decisions. Mehanna et al.[78] emphasized that discordance between p16 status and actual HPV presence can significantly influence treatment outcomes, especially in cases where treatment de-escalation is being considered. Moreover, accumulating evidence points to substantial biological and clinical differences between HPV16 and non-HPV16 OPC, with the latter often demonstrating poorer survival outcomes and less predictable responses to standard therapies. As such, relying solely on p16 IHC may not provide a comprehensive assessment of HPV-related oncogenesis. To overcome these limitations and improve diagnostic precision, the integration of HPV genotyping particularly through DNA- or RNA-based molecular assays is increasingly recommended. By combining p16 IHC with HPV genotyping, clinicians can achieve a more accurate classification of HPV-mediated disease, enabling more personalized treatment planning and better patient stratification in both routine practice and clinical trials[75].

Clinically, HPV-non16 oropharyngeal squamous cell carcinoma (OPSCC) presents with distinct outcomes compared to HPV16-positive cases, as supported by several clinical trials and retrospective studies. A systematic review and meta-analysis by Shenker et al.[76] revealed that the 5-year overall survival (OS) for HPV16-positive OPSCC was significantly higher at 83.4%, compared to 69.3% for non-HPV16 cases (log odds ratio: −0.54; P=0.008), indicating a marked survival advantage for patients infected with HPV16. Similarly, the 5-year disease-free survival (DFS) was 77.6% in the HPV16 group versus 64.6% in the non-HPV16 group, although this difference did not reach statistical significance (P=0.063), suggesting that HPV16-related tumors may be more responsive to standard therapies or inherently less aggressive. Further supporting this trend, a multicenter study with a median follow-up of 43 months reported that 3-year OS for HPV16-positive OPSCC was 87.7%, compared to 73.6% for patients with non-HPV16 genotypes. Likewise, the 3-year DFS was 82.9% versus 68.7%, respectively, though neither comparison achieved statistical significance (P=0.11 for OS, P=0.16 for DFS) (ref.[76]). These findings indicate a consistent pattern of poorer outcomes among non-HPV16 OPSCC patients across different time points and study populations[79]. Additionally, patients with non-HPV16 genotypes such as HPV18, 33, and 35 were reported to have lower viral loads and reduced p16 expression, which are factors that may correlate with poorer treatment response and less favorable prognosis[80]. This genotype-specific difference highlights the importance of HPV subtyping in the prognostic assessment and therapeutic stratification of OPSCC, as non-HPV16 genotypes may necessitate more aggressive or alternative treatment approaches due to their comparatively unfavorable clinical behavior.

Trials such as ECOG E1308 and OPTIMA have explored reduced-dose radiation or chemoradiotherapy (CRT) following favorable induction chemotherapy (IC) responses in HPV-positive oropharyngeal squamous cell carcinoma (OPSCC) patients. These studies demonstrated that patients who responded well to IC could receive de-intensified treatment with comparable two-year progression-free survival (PFS) and overall survival (OS) outcomes. For instance, in ECOG E1308, patients with complete clinical response at the primary tumor site after IC were treated with reduced-dose IMRT (54 Gy), resulting in a two-year PFS of 80% and OS of 94%, while also showing reduced long-term toxicities such as dysphagia and xerostomia. Similarly, the OPTIMA trial stratified patients based on risk features and response to IC, where low-risk patients who received de-intensified therapy still achieved a two-year PFS of 95%, underscoring the feasibility of treatment de-escalation in select cohorts[81].

However, the presence of high-risk features, such as advanced T-stage (e.g., T4 tumors), N3 nodal disease, or smoking history >10 pack-years, continues to be a significant negative prognostic factor despite favorable HPV status. These high-risk factors have been associated with increased locoregional recurrence and reduced survival, indicating that the current AJCC 8th edition staging system which groups many HPV-positive tumors into lower stages based largely on nodal involvement may not adequately capture the biological and clinical heterogeneity seen with different HPV genotypes or tumor behaviors[82]. Specifically, T4 disease has consistently been linked with inferior outcomes across multiple studies, suggesting a need for a more nuanced staging system that accounts for primary tumor burden and HPV genotype to better guide therapy and prognosis[83]. Table 5, provide the comparison of clinical and biological characteristics between HPV and non-HPV 16 Oropharyngeal carcinoma. Further research into the molecular and clinical distinctions among HPV-positive subtypes is essential to optimize outcomes and inform future staging and treatment paradigms.

BIOMARKERS FOR PREDICTING RESPONSE TO IMMUNE CHECKPOINT INHIBITORS IN HPV-POSITIVE OPC

Numerous biomarkers have been investigated to predict patient response to immune checkpoint inhibitors (ICIs) in oropharyngeal cancer (OPC), particularly in HPV-positive cases, which present distinct immunological features compared to their HPV-negative counterparts. Among these, programmed death-ligand 1 (PD-L1) ex-

Table 5. Comparison of clinical and biological characteristics between HPV and non-HPV 16 oropharyngeal carcinoma.

Aspect	HPV16-Positive OPC	Non-HPV16-Positive OPC	Ref.
Prevalence among HPV-OPC	Most common subtype	Less frequent	
p16 Expression	High concordance with p16 positivity	Lower p16 expression	
Treatment response	Excellent response to chemoradiotherapy	Variable or poorer response	
Overall survival (OS)	Higher (e.g., 5-year OS > 80%)	Lower and more variable	
Progression-free survival (PFS)	Higher	Lower trend	
Recurrence	Lower recurrence rates	Higher recurrence risk	
Metastatic pattern	Mostly locoregional recurrence	Locoregional + higher distant metastasis risk	
Risk factors impact	Less influenced by smoking and alcohol	More affected by traditional risk factors	
Staging (AJCC 8th Edition)	More favorable prognosis stratification	May require revised staging system	
Recommended testing	p16 IHC + HPV genotyping (confirmatory)	Essential to combine both p16 and genotyping	
Clinical trials for De-escalation	ECOG E1308, OPTIMA – positive trend	De-escalation not widely tested	84

pression remains the most extensively studied. High PD-L1 levels, measured using the combined positive score (CPS), are generally associated with enhanced clinical responses to anti-PD-1/PD-L1 therapies such as pembrolizumab and nivolumab. For example, in the pivotal phase III KEYNOTE-048 trial, pembrolizumab monotherapy significantly improved overall survival in recurrent/metastatic head and neck squamous cell carcinoma (HNSCC) patients with a CPS ≥1, particularly in those with CPS ≥20 (ref.[23]). Despite this, PD-L1 is not a definitive predictor, as some PD-L1-negative tumors still respond to ICIs, indicating the need for additional biomarkers[85].

Another promising biomarker is tumor mutational burden (TMB), which reflects the number of somatic mutations per coding area of a tumor genome. Higher TMB may lead to increased neoantigen formation, promoting immune recognition and responsiveness to ICIs (ref.[72]). However, HPV-positive OPCs typically exhibit lower TMB than HPV-negative tumors, likely due to the viral origin of antigens rather than mutational events. This suggests that viral antigen-driven immune responses, rather than mutational load, contribute more significantly to ICI efficacy in HPV-positive cases[29]. The tumor microenvironment (TME), particularly the infiltration of tumor-infiltrating lymphocytes (TILs), has also emerged as a critical determinant of response. A high density of CD8+ cytotoxic T cells, along with a favorable CD8+/Treg ratio, has been consistently associated with improved responses to checkpoint blockade[85]. HPV-positive OPCs often exhibit a Th1-skewed cytokine profile, with elevated levels of IL-2, IFN-γ, and TNF-α, indicative of a more immunologically active and responsive environment[74].

Further supporting this, interferon-gamma (IFN-γ) gene signatures have shown predictive utility. Tumors enriched in IFN-γ-responsive genes such as CXCL9, CXCL10, and IDO1 demonstrate increased immune infiltration and improved responses to ICIs (ref.[86]). These IFN-γ gene signatures reflect an inflamed TME that facilitates immune checkpoint blockade, commonly observed in HPV-positive OPC. In addition to PD-L1 and TILs, T-cell receptor (TCR) clonality is gaining attention as a biomarker of immune responsiveness. High TCR clonality within TILs implies a focused and antigen-driven immune response. This is particularly relevant in HPV-positive tumors, where viral antigens serve as potent non-self-targets, stimulating clonal expansion of T cells. High intratumoral TCR clonality has been correlated with improved outcomes following ICI therapy[87].

More recently, the microbiome, particularly the gut and oral microbiota, has emerged as an influential factor in modulating immunotherapy outcomes. The gut microbiota can influence systemic immunity through T-cell activation, pattern recognition receptor signaling, and microbial metabolite production. Certain commensals, including *Akkermansia muciniphila* and *Enterococcus hirae*, have been associated with enhanced ICI responses. Fecal microbiota transplantation (FMT) from ICI-responsive hosts has been shown to improve antitumor immunity in non-responders in preclinical models[86]. In clinical settings, use of antibiotics prior to or during ICI therapy negatively correlates with survival outcomes in cancers such as melanoma, renal, and lung cancers, further reinforcing the importance of microbiota composition. In the context of HNSCC, changes in the oral microbiome have been implicated in disease progression and immune modulation. Studies have shown an overrepresentation of *Fusobacterium* species and a depletion of *Streptococcus spp*. in tumor tissues. Specifically, increased abundance of *Fusobacterium periodonticum* and reduced levels of *Streptococcus mitis* and *Prevotella pasteri* have been linked to advanced stages of oral squamous cell carcinoma[86]. Lifestyle factors such as alcohol, tobacco, and oral hygiene practices may further modulate these microbial communities, thereby influencing immune responses and potentially affecting ICI efficacy.

To further personalize treatment, liquid biopsy-based biomarkers, including circulating tumor DNA (ctDNA) and immune-related gene signatures, are under exploration[88]. These tools offer real-time, non-invasive insights into tumor dynamics, response, and resistance mechanisms. Moreover, combining ICIs with targeted agents, radiation, or therapeutic HPV vaccines is being investigated to potentiate antitumor immunity in biomarker-defined patient populations[78]. Taken together, while PD-L1 remains a cornerstone biomarker in the immunotherapy landscape, incorporating a multidimensional panel including IFN-γ signatures, TCR clonality, TIL profiles, and microbiota composition may yield a more accurate

prediction of therapeutic outcomes in HPV-positive OPC.

CHALLENGES AND LIMITATIONS IN IMMUNOTHERAPY FOR HPV-RELATED OPC

Immunotherapy has emerged as a promising treatment modality for human papillomavirus (HPV)-related oropharyngeal cancer (OPC), particularly with the advent of immune checkpoint inhibitors. Despite encouraging outcomes in a subset of patients, several challenges and limitations hinder its broad clinical success.

Tumor immune evasion and suppressive microenvironment

HPV-related OPCs are generally recognized as immunogenic due to the constant expression of viral oncoproteins E6 and E7, which are foreign to the host immune system. These viral proteins, however, also play a key role in helping tumor cells avoid immune surveillance[66]. For example, E6 and E7 have been implicated in disrupting the normal function of major histocompatibility complex (MHC) class I molecules, which are essential for presenting antigens to cytotoxic T cells. This interference reduces the visibility of tumor cells to the immune system, weakening the anti-tumor response[89]. The development of immune evasion mechanisms is a major challenge in HPV-driven squamous cell carcinomas, as these tumors typically evolve over several years within the host. Over time, they adopt a variety of strategies to suppress both innate and adaptive immune responses. One such strategy includes impairing antigen processing pathways or reducing MHC expression, which diminishes the effectiveness of cytotoxic T lymphocyte (CTL) targeting[56]. Moreover, HPV-infected tumor cells can influence the local tissue environment, fostering the release of immunosuppressive cytokines by stromal cells, and promoting the accumulation of regulatory T cells (Tregs), M2-like macrophages, and myeloid-derived suppressor cells (MDSCs) (ref.[90]). These changes lead to a tumor microenvironment (TME) that is highly suppressive and unfavorable for anti-tumor immunity.

Evidence from transgenic mouse models expressing HPV16 E7 supports the existence of these immune evasion strategies. In these models, extensive immune modulation such as altered cytokine profiles and suppressed antigen presentation has been observed in hyperproliferative epithelial tissue. Interestingly, when E7 expression occurs alongside a mutation that prevents epithelial proliferation, these immune evasion traits are significantly diminished. This suggests that local immunosuppression may be more closely linked to tumor cell proliferation rather than the presence of viral antigens alone[91]. Additionally, human genetic studies have shown that progression from persistent HPV infection to precancerous lesions is strongly influenced by individual variations in MHC genes. Certain MHC alleles are associated with a greater risk of disease progression, indicating that the ability of the immune system to recognize HPV-derived antigens is, at least in part, genetically determined[92]. These findings suggest that deficits in T cell responses to HPV oncoprotein shaped by MHC-restricted antigen presentation could reduce the effectiveness of immunotherapies that rely on adaptive immunity. In summary, the immune escape observed in HPV-positive OPC arises from a combination of disrupted antigen presentation, an immunosuppressive tumor microenvironment, and host genetic factors. These multifactorial barriers present significant challenges to the success of immunotherapy and highlight the need for comprehensive strategies that address both tumor-intrinsic and host-driven mechanisms of immune resistance.

Variable and limited response to immune checkpoint inhibitors

Immune checkpoint inhibitors (ICIs), particularly those targeting the PD-1/PD-L1 axis, have introduced new therapeutic possibilities in the management of recurrent and metastatic HPV-positive oropharyngeal cancer (OPC). Clinical trials have demonstrated their ability to produce durable responses in a subset of patients, with landmark studies such as that by Ferris[70] reporting objective response rates (ORRs) of approximately 15% to 20%. Despite these encouraging outcomes, the majority of patients derive limited or no benefit from checkpoint blockade, underscoring a pressing need to better understand and overcome resistance mechanisms. One major limitation lies in the heterogeneous immune landscape of HPV-related OPC. While some tumors display a "hot" phenotype with abundant CD8+ T cell infiltration and high PD-L1 expression predictors of better ICI responsiveness many others exhibit "cold" or "immune-excluded" phenotypes. These immune-deserted tumors are poorly infiltrated by effector immune cells, making them less responsive to checkpoint inhibition due to the lack of pre-existing antitumor immune activity[93].

Moreover, primary resistance to ICIs is often driven by several intrinsic and extrinsic factors. Tumor-intrinsic mechanisms may include defects in interferon signaling, loss of antigen presentation machinery (e.g., B2M or MHC class I mutations), and constitutive activation of oncogenic pathways such as WNT/β-catenin, which collectively impair the recruitment and function of T cells within the tumor microenvironment. Additionally, host-derived immunosuppressive elements such as regulatory T cells (Tregs), MDSCs, and immunoregulatory cytokines (e.g., TGF-β, IL-10) further compromise the immune response, creating an unfavorable milieu for checkpoint blockade to function effectively[94].

Acquired resistance also poses a considerable challenge in patients who initially respond to ICIs. Over time, tumor cells may adapt through upregulation of alternative immune checkpoints (e.g., TIM-3, LAG-3), increased immunosuppressive metabolite production (such as IDO), or clonal evolution that results in the emergence of antigen-loss variants[49]. These mechanisms enable tumor escape from immune surveillance, thereby limiting the durability of response. Collectively, the modest response rates and the emergence of resistance both primary and

acquired highlight the need for rational combination strategies. These may include pairing ICIs with radiation, therapeutic vaccines, epigenetic modulators, or agents that remodel the tumor microenvironment to convert "cold" tumors into "hot" ones[38].

Lack of predictive biomarkers

One of the central challenges in optimizing immunotherapy for HPV-related oropharyngeal cancer (OPC) is the absence of robust and reliable biomarkers that can accurately predict clinical response. Although programmed death-ligand 1 (PD-L1) expression and tumor mutational burden (TMB) are widely utilized as surrogate indicators, their predictive value in HPV-positive OPC is inconsistent and often unreliable. PD-L1 immunohistochemistry, for instance, has been employed as a biomarker to guide checkpoint inhibitor therapy, with the assumption that higher expression correlates with improved response. However, clinical observations indicate that this correlation is far from absolute. Patients with low or even undetectable PD-L1 expression may still experience durable responses, while those with high expression sometimes exhibit resistance or minimal therapeutic benefit[30]. This lack of concordance diminishes the utility of PD-L1 as a standalone predictive marker in HPV-associated tumors.

Similarly, TMB another emerging biomarker has demonstrated limited application in the context of virally driven cancers. Unlike many smoking-related head and neck cancers, HPV-positive tumors tend to exhibit relatively low mutational burdens, yet they often remain immunogenic due to the presence of viral antigens such as E6 and E7. This suggests that TMB may not fully capture the antigenic complexity or the immunological potential of these tumors. Beyond these limitations, HPV-associated OPC presents unique immunological features that further complicate biomarker development. For example, immune activation may be influenced more by the quality of the tumor microenvironment, the spatial distribution of immune infiltrates, and the expression of viral oncoproteins rather than by PD-L1 levels or mutation load alone. In addition, emerging evidence points to the potential utility of alternative biomarkers such as gene expression signatures (e.g., interferon-gamma response genes), immune cell composition and localization, T cell receptor diversity, and circulating immune-related molecules as more informative predictors of immunotherapy success[3].

Thus, there is a critical need to move beyond conventional markers and develop integrated biomarker platforms that reflect the dynamic tumor-immune interplay in HPV-driven malignancies. Multimodal approaches combining genomic, transcriptomic, proteomic, and spatial immune profiling may hold the key to identifying actionable biomarkers capable of guiding personalized immunotherapy in HPV-positive OPC (ref.[95]).

Tumor heterogeneity

Despite being categorized as a distinct molecular and clinical subgroup, HPV-positive oropharyngeal cancers (OPCs) are far from uniform. A growing body of evidence underscores the existence of both intertumoral and intratumoral heterogeneity within HPV-associated OPCs, which poses significant challenges to immunotherapy responsiveness and treatment personalization. At the intertumoral level, key differences exist in the status of viral genome integration. In some tumors, the HPV genome is episomal, while in others it is integrated into the host genome – a distinction that can influence viral gene expression, genomic instability, and host immune responses. Integrated HPV is often associated with dysregulated expression of viral oncoproteins such as E6 and E7, which may alter immune visibility and therapeutic targets[64].

In addition to viral integration patterns, heterogeneity in immune gene expression signatures such as levels of interferon-stimulated genes, chemokines, and immune checkpoints further stratifies tumors into immune “hot” or “cold” phenotypes. Tumors classified as immune “cold” tend to have reduced infiltration of cytotoxic T lymphocytes and are typically less responsive to checkpoint inhibitors, whereas “hot” tumors show higher immune activity and a more favorable response profile[94]. This immunological diversity, even among HPV-positive tumors, contributes to variability in clinical outcomes. Intratumoral heterogeneity adds another layer of complexity. Within a single tumor mass, different cellular subpopulations may exhibit distinct phenotypes, including variations in antigen presentation, mutational burden, and local cytokine production. These differences may allow some tumor regions to evade immune recognition or resist immunotherapeutic pressure, ultimately leading to treatment failure or relapse[79].

Host genetic variability also plays a critical role. Differences in human leukocyte antigen (HLA) alleles, immune receptor polymorphisms, and other germline factors can shape the immune landscape of the tumor and influence the effectiveness of antigen-specific therapies[89]. Altogether, this heterogeneity makes stratifying patients for immunotherapy particularly challenging. It underscores the need for comprehensive tumor profiling strategies integrating genomic, transcriptomic, and spatial immune analyses to better understand tumor behavior and tailor immunotherapeutic regimens accordingly. Overcoming the barriers imposed by tumor heterogeneity will be essential for maximizing the efficacy of immunotherapy in HPV-positive OPC.

Immune-related adverse events (irAEs)

While immune checkpoint inhibitors (ICIs) have transformed the therapeutic landscape of HPV-related oropharyngeal cancer (OPC), their use is frequently accompanied by immune-related adverse events (irAEs), which can compromise treatment safety and continuity[96]. These irAEs arise from the nonspecific activation of the immune system, leading to inflammation and damage in normal tissues. The spectrum of irAEs is broad, affecting multiple organ systems. Common manifestations include dermatologic toxicities (rash, pruritus), gastrointestinal disturbances (colitis, diarrhea), hepatic inflammation (transaminitis, hepatitis), and endocrine dysfunctions (hypothyroidism, hypophysitis, adrenal insufficiency) (ref.[97]). Less frequently, patients may develop pneumoni-

tis, nephritis, myocarditis, or neurologic complications, which may be life-threatening if not promptly recognized and managed[34].

Although the incidence and severity of irAEs in head and neck squamous cell carcinoma (HNSCC), including HPV-positive OPC, are generally lower than in other malignancies such as melanoma or non-small cell lung cancer, they still represent a critical concern. The unpredictable nature of irAEs requires vigilant monitoring and a multidisciplinary approach for early identification and management. In severe cases, immunotherapy must be discontinued, and systemic corticosteroids or other immunosuppressants may be required, potentially diminishing the antitumor efficacy of ICIs (ref.[63]). Furthermore, the onset of irAEs can vary widely, from days to months after treatment initiation, and some effects may persist long after therapy cessation. This delayed presentation poses additional challenges for clinicians and highlights the need for long-term follow-up care. The occurrence of irAEs has also been paradoxically associated with favorable outcomes in some studies, suggesting a link between immune activation and therapeutic benefit. However, this association remains controversial and underscores the importance of identifying predictive markers for both efficacy and toxicity to optimize treatment decisions. While irAEs are a manageable yet significant limitation of immunotherapy, they underscore the necessity for personalized treatment plans, standardized management guidelines, and patient education to ensure both efficacy and safety in HPV-related OPC immunotherapy.

Economic and logistical barriers

The integration of immune checkpoint inhibitors (ICIs) and other personalized immunotherapy strategies into clinical practice has brought about significant therapeutic advancements for patients with HPV-related oropharyngeal cancer (OPC). However, these treatments are accompanied by substantial economic and infrastructural challenges that hinder their widespread adoption, particularly in resource-limited settings. The cost of immunotherapy remains prohibitively high, with checkpoint inhibitor therapies such as pembrolizumab or nivolumab often exceeding USD 100,000 per patient annually. Reflecting this economic burden, overall spending and utilization of immune checkpoint inhibitors (ICIs) have risen exponentially over the past decade, with expenditures increasing from $2.8 million in 2011 to $4.1 billion in 2021 (ref.[98]). These expenses encompass not only the drug itself but also the associated costs of diagnostic testing, biomarker profiling, supportive care, and management of immune-related adverse events. Such financial burden places immense strain on healthcare systems and insurance frameworks, especially in low- and middle-income countries where access to advanced therapies is already limited.

Moreover, logistical challenges further complicate equitable access. Personalized immunotherapy often requires sophisticated infrastructure, including genomic sequencing facilities, immune monitoring platforms, and specialized oncology care teams. Many healthcare institutions, particularly those in rural or under-resourced areas, lack the necessary equipment and trained personnel to deliver these therapies safely and effectively. In addition, the prolonged treatment duration and the need for frequent monitoring visits can impose indirect costs on patients and caregivers, such as travel expenses and lost wages. These socioeconomic barriers contribute to disparities in treatment access and outcomes, raising ethical concerns regarding healthcare equity and the global applicability of immunotherapy advances[96]. Addressing these challenges requires concerted efforts to reduce the cost of novel agents, develop cost-effective delivery models, and expand access to molecular diagnostic tools. International collaborations, public-private partnerships, and policy reforms aimed at health system strengthening will be essential to ensure that the benefits of immunotherapy reach a broader and more diverse patient population.

Therapeutic vaccine limitations

Therapeutic vaccines designed to elicit robust immune responses against HPV-specific antigens particularly the E6 and E7 oncoproteins are an attractive approach in the treatment of HPV-related oropharyngeal cancer (OPC). These viral proteins, consistently expressed in tumor cells and absent in normal tissues, represent ideal targets for immune-based interventions. However, translating the promise of therapeutic vaccination into meaningful clinical benefit has proven challenging[98]. While preclinical studies have demonstrated the ability of these vaccines to activate antigen-specific cytotoxic T lymphocyte responses and reduce tumor burden, the results from early-phase clinical trials have been less encouraging. Limited vaccine-induced immunogenicity in human subjects remains a significant hurdle. Factors such as pre-existing immune tolerance, antigen processing deficits, and variability in human leukocyte antigen (HLA) presentation influence the capacity of these vaccines to generate effective antitumor immunity[99].

Another key limitation lies in the immunosuppressive tumor microenvironment (TME) characteristic of HPV-positive OPC. The presence of regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), and immunomodulatory cytokines contributes to an environment that actively suppresses vaccine-induced immune responses. Even in cases where T cell activation is achieved, these cells may become functionally exhausted or sequestered away from the tumor site due to inhibitory signals within the TME. To overcome these barriers, current research is focused on combination strategies that pair therapeutic vaccines with immune checkpoint inhibitors (ICIs) or potent adjuvants. ICIs may relieve T cell exhaustion and enhance the functionality of vaccine-primed immune cells, while adjuvants can amplify the innate immune signaling required to initiate effective adaptive responses. Additionally, novel delivery platforms such as mRNA-based vaccines, dendritic cell vaccines, and viral vectors are being evaluated for their ability to improve antigen presentation and immunogenicity[38,74].

Despite the challenges, therapeutic vaccines remain a promising component of a multimodal immunotherapeutic approach in HPV-associated cancers. Future suc-

cess will likely depend on rational design incorporating immunologic insights, careful patient selection based on biomarkers, and strategic combination with other immunomodulatory agents.

FUTURE DIRECTIONS

The future of immunotherapy for HPV-positive oropharyngeal cancer (OPC) is increasingly optimistic, fueled by rapid advancements in next-generation immune-based strategies, precision medicine, and computational technologies. These developments aim to address the current therapeutic limitations by enhancing efficacy, specificity, and personalization of treatment.

Next-generation immunotherapies and emerging targets

Beyond the well-established PD-1/PD-L1 axis and CTLA-4, novel immune checkpoint molecules such as T cell immunoglobulin and mucin-domain containing-3 (TIM-3), lymphocyte-activation gene 3 (LAG-3), and T cell immunoreceptor with Ig and ITIM domains (TIGIT) have emerged as promising targets for reactivating exhausted T cells and augmenting anti-tumor responses[99]. Clinical trials are currently evaluating the efficacy of inhibitors against these checkpoints, both as monotherapies and in combination with existing immune checkpoint inhibitors. Innovative therapeutic modalities such as bispecific T cell engagers and chimeric antigen receptor (CAR) T cells tailored to recognize HPV-derived antigens like E6 and E7 are also being explored. These platforms offer heightened tumor specificity and the ability to redirect immune cells with precision toward virally transformed cancer cells[79]. Importantly, the co-administration of therapeutic HPV vaccines with immune checkpoint blockade may yield synergistic effects, simultaneously priming tumor-specific T cells and relieving immune suppression.

Personalized medicine and artificial intelligence integration

The shift toward individualized immunotherapy is increasingly supported by the integration of high-throughput technologies that generate comprehensive genomic, transcriptomic, and proteomic profiles. These molecular characterizations enable the identification of predictive biomarkers and immune signatures that inform patient selection and guide treatment decisions[51]. Artificial intelligence (AI) and machine learning algorithms are being harnessed to interpret multidimensional data from sequencing platforms, digital pathology, and imaging tools. These computational approaches facilitate pattern recognition, outcome prediction, and treatment optimization across heterogeneous patient populations[100]. The incorporation of AI into clinical workflows not only enhances diagnostic precision but also accelerates therapeutic discovery and the design of adaptive immunotherapeutic protocols. Together, these emerging innovations are poised to redefine the landscape of HPV-positive OPC treatment, moving toward more effective, durable, and tailored interventions that account for individual tumor biology and immune contexture.

CONCLUSION

Immunotherapy has redefined the therapeutic landscape for HPV-related OPC, offering a novel modality that harnesses the immune system to achieve sustained tumor control. However, challenges including immune evasion, heterogeneous response rates, adverse events, and limited predictive biomarkers necessitate further innovation. Future progress hinges on the development of combination strategies involving novel immunotherapeutic agents, enhancement of HPV-specific immune responses, and the application of precision medicine frameworks. As research continues to bridge the gap between bench and bedside, the vision of highly effective, personalized, and minimally toxic immunotherapy for HPV-positive OPC is increasingly within reach. Through interdisciplinary collaboration and translational research, immunotherapy stands poised to transform the long-term outcomes and quality of life for patients with HPV-driven oropharyngeal cancers.

Search strategy and selection criteria

A comprehensive literature search was conducted to identify studies evaluating the role of immunotherapy in oropharyngeal cancer (OPC), with a particular focus on the influence of HPV status and the development of predictive biomarkers. The databases PubMed, Scopus, and Web of Science were searched for relevant publications from January 2010 to April 2025. The search employed combinations of keywords and MeSH terms, including “oropharyngeal cancer,” “HPV,” “immunotherapy,” “checkpoint inhibitors,” “monoclonal antibodies,” “cancer vaccines,” and “T cell therapy.” Only peer-reviewed original articles, clinical trials, and reviews published in English were considered. Studies were included if they specifically addressed immunotherapeutic approaches in OPC, discussed HPV-related response variations, or examined clinical outcomes and biomarker relevance. Data extraction was performed systematically, and studies were categorized based on immunotherapy type, HPV status, clinical outcomes, and biomarker significance.

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